LMMG New Medicine Recommendation

Fluorouracil + salicylic acid (Actikerall®), imiquimod (Zyclara®) and ingenol (Picato®▼) for the treatment of actinic keratoses

LMMG Recommendation:

Amber 0: Ingenol mebutate (Picato®▼) is recommended for the treatment of non-hyperkeratotic, non-hypertrophic AK affecting an area of ≤25cm^2. Ingenol mebutate offers a convenient, short treatment duration and based on current list prices is marginally less costly than diclofenac 3% gel.

Black: Fluorouracil 0.5% + salicylic acid 10% (Actikerall®) is not recommended for the treatment of AK. Limited data suggest it has comparable efficacy to other agents and there is little robust evidence of superior efficacy, safety or convenience versus fluorouracil 5% cream, which has a lower list price.

Black: Imiquimod 3.75% (Zyclara®) is not recommended for the treatment of AK. There is little robust evidence to justify its significantly greater list price compared with other topical treatments.

Summary of supporting evidence:

- A Cochrane review concluded that established topical treatments (diclofenac 3%, imiquimod 5%, 5-fluorouracil 5%) appear to have comparable efficacy and differ with respect to adverse events, but also notes that more direct comparative data are required to determine the best therapeutic approach.
- Comparative data for newer agents is limited to a single trial of 5-FU/SA against diclofenac 3%. This was the only trial of the newer agents to have confirmed lesion clearance histologically. However, the majority of lesions treated in that trial were grade II (hyperkeratotic) for which the Primary Care Dermatology Society indicates diclofenac 3% is the least suitable of the topical treatment options. It is therefore unclear that diclofenac 3% was the most relevant comparator.
- All newer treatments achieved significantly greater complete clearance rates at 8 weeks follow-up compared with placebo (NNTs of 3 or 4). Indirect comparisons of available trial data are reported to show no statistically significant differences between the newer treatments; however, due to many differences in trial designs and endpoint assessment these results are subject to considerable uncertainty.
- All topical treatments are associated with local application site reactions. This may have revealed treatment assignment and biased subjective efficacy assessment in placebo-controlled trials.
- Recurrence rates at 12 months among patients achieving complete AK lesion clearance in the trials of imiquimod 3.75% and ingenol mebutate were high (>50%). Details on recurrence rates with 5-FU/SA are lacking. No data on re-treatment are available.
- The aim of treating AK lesions is to prevent progression to squamous cell carcinoma. Longer term data for newer and established treatments is lacking in this regard.

- Licensed indications of topical treatments differ. The duration and frequency of treatment application for each of the different topical treatments may be expected to influence adverse events, treatment adherence and treatment preferences.

Author:	**Warren Linley**	
Reviewer:	**Brent Horrell**	
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Clinical Reference Group (if appropriate)	**Skin**	
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Details of Review

Name of medicine(s) (generic & brand name)**:** Fluorouracil + salicylic acid (Actikerall®), imiquimod (Zyclara®) and ingenol (Picato®▼)
Strength(s) and Form(s): Fluorouracil 0.5% + salicylic acid 10% (Actikerall®): 25ml solution Imiquimod 3.75% (Zyclara®): 28 x single-use sachets cream Ingenol mebutate150mcg/g (Picato®▼): 3 x 0.47g tubes gel Ingenol 500mcg/g (Picato®▼): 2 x 0.47g tubes gel
Relevant licensed indications: Fluorouracil 0.5% + salicylic acid 10% (Actikerall®): slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (Olsen grade I/II) in immunocompetent adult patients Imiquimod 3.75% (Zyclara®): clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis (AK) of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate Ingenol 150mcg/g and 500mcg/g (Picato®▼): non-hyperkeratotic, non-hypertrophic actinic keratosis in adults
Reason for Review: LMMG request following horizon scanning; newer treatments recently available.
Proposed use (if different from or in addition to licensed indication above): As above

Background and context

Actinic keratoses are common, sun-induced, scaly or hyperkeratotic lesions. They often regress spontaneously but there is a low risk of these progressing to squamous cell carcinoma (around 1 in 1000 lesions per annum), which increases with the number of actinic keratotic (AK) lesions an individual has (e.g. with an average of 7.7 AK lesions the risk of one transforming in 10 years is 10%). It is difficult to predict which AK lesions may progress. Patients who are immunosuppressed, have a past history of skin cancer, have extensive sun damage, previous history of phototherapy, are very young, or with xeroderma pigmentosum are at high risk and should be referred to specialist care. For other patients at lower risk, treatment with topical agents in primary care may be considered [1,2].

A 2012 treatment pathway by the Primary Care Dermatology Society recommends treatment with diclofenac 3% gel (Solaraze®) ahead of other topical agents for grade I AK (single or few lesions, better felt than seen). For grade II AK (hyperkeratotic lesions that are moderately thick, easily felt and seen), 5% fluorouracil cream (Efudix®) , imiquimod 5% cream (Aldara®), and 0.5% fluorouracil + 10% salicylic acid solution (Actikerall®) are recommended ahead of Solaraze® as treatment options [2]. Since this pathway was published, ingenol gel (Picato®) and imiquimod 3.75% cream (Zyclara®) have become available.

Following horizon scanning, LMMG requested a review of newer topical agents for the treatment of AK. This review considers the evidence for newer topical agents in the context of established agents such as diclofenac 3% (Solaraze®) gel, fluorouracil 5% (Efudix®) cream and imiquimod 5% (Aldara®) cream. Topical agents used in photodynamic therapy are not considered.

Evidence review

This evidence review draws largely on the comprehensive overviews of key efficacy and safety data included in the advice on Actikerall® and Picato® issued by the Scottish Medicines Consortium (SMC) [3,4] and All Wales Medicines Strategy Group (AWMSG) [5,6], a 2012 Cochrane review of treatments for actinic keratosis [7], and a 2013 review of newer topical agents by the Regional Drug and Therapeutics Centre (RDTC) at Newcastle [8].

Summary of Efficacy Data:

Established treatments: diclofenac 3%, fluorouracil 5% and imiquimod 5%

Diclofenac 3%:
The Cochrane review estimated the relative risk of 'participant complete clearance' with diclofenac 3% in hyaluronic acid 2.5% compared with vehicle/placebo. Based on three trial comparisons (n=420), 3% diclofenac in 2.5% hyaluronic acid significantly improved rates of complete clearance of all target and new lesions at 30 days follow-up after 30, 60 or 90 days treatment compared with placebo/vehicle control (RR 2.46, 95% CI 1.66 to 3.66; NNT=5) [7]. The RDTC report identified a review of 18 clinical trials of various designs, conducted since 2000, that collectively support the efficacy of 3% diclofenac in the treatment of AK [8].

Fluorouracil 0.5% and 5%:
No relevant trials of Fluorouracil 5% compared against placebo were identified in the Cochrane review [7]. Three trial comparisons (n=522) of fluorouracil 0.5% and placebo indicate the lower strength cream significantly improved AK clearance rates at four week follow-up after one, two or four week treatment (RR 8.86, 95% CI: 3.67 to 21.44; NNT=9). The efficacy of the lower strength fluorouracil 0.5% cream was compared to fluorouracil 5% cream in one within-participant study. The 0.5% cream was applied once daily on one side of the face, and the 5% cream was applied twice daily on the other side for four weeks, with assessment performed four weeks after the end of treatment. Due to the intra-individual design of the study, no analysis could be performed for the 'participant complete clearance' outcome; however, although a similar total clearance rate was obtained for the two treatments (approximately 43%), the mean reduction was significantly greater for the lower strength cream (67% vs. 47%; p=0.044). There was possible performance and reporting bias associated with this study. [7]. The RDTC report refers to another within-participant study, in which 29 patients applied diclofenac 3% gel to one side of the face twice daily for 90 days and fluorouracil 5% to the other side starting at day 62, for the remaining 28 days. At the trial end, 89% of lesions had cleared with diclofenac 3% compared with 98% of lesions with fluorouracil [8].

Imiquimod 5%:
The Cochrane review estimated the relative risk of 'participant complete clearance' for imiquimod 5% compared with vehicle/placebo. Based on nine trial comparisons (n=1,871), imiquimod 5% significantly improved rates of complete clearance compared with placebo/vehicle control (RR 7.70; 95% CI 4.63 to 12.79; NNT=5). One small unblinded trial that used the usual treatment regimen for imiquimod 5% found this to be comparable to fluorouracil 5% for participant complete clearance (RR 0.88; 95% CI 0.73 to 1.06); however, the percentage of participants with a general cosmetic outcome assessed as excellent by the investigator was significantly better for imiquimod (21/26 = 81%) than 5-fluorouracil (81% vs 4%; RR 19.38: 95%CI 2.82 to 133.26; NNT=1) [7].

Collectively, the Cochrane review concluded that topical treatments were similarly effective, but their associated adverse events may different (see below). More direct comparisons between these treatments are needed to determine the best therapeutic approach [7].

Newer treatments: Fluorouracil 0.5% + salicylic acid 10%, imiquimod 3.75%, ingenol
Table 1 provides an overview of key trial data for newer topical treatments used as recommended by their respective Summaries of Product Characteristics.

Fluorouracil 0.5% + salicylic acid 10%:
Based on one phase III, double-blind RCT, rates of histologically confirmed clearance of AK lesions (60% grade II) on the face, forehead or bald scalp 8 weeks following treatment completion were statistically significantly greater with 5-FU/SA than with diclofenac (72.0% vs. 59.1%, p<0.01; NNT=8) in the per protocol population [5]. Reduction in secondary endpoints of mean lesion area and change in lesion count from baseline to week 20 were also reported to be significantly superior for 5-FU/SA. The proportion of patients and clinicians rating clinical improvements at 20 weeks as 'good' or 'very good' was significantly greater for 5-FU/SA than for diclofenac. Longer term follow up was not available from this trial [5]. The RDTC report notes data from an uncontrolled trial that is reported to show that the majority of lesions treated with 5-FU/SA had not returned at 12 months [8], but the data are available as a poster presentation only.

Imiquimod 3.75%:
Based on pooled data from two identical double-blind RCTs, rates of investigator assessed clearance of AK lesions on the face or scalp 8 weeks following treatment completion were statistically significantly greater with imiquimod 3.75% than with placebo (35.6% vs. 6.3%; p<0.001; NNT=3). Rates for the secondary endpoints of partial (≥75%) clearance (59.4% vs. 22.6%) also significantly favoured imiquimod 3.75%. In patients achieving complete clearance in these two RCTs and two other RCTs that used a different treatment regimen, 40.5% remained clear at 12 months follow-up [8]. The Cochrane review found no statistically significant differences in the efficacy of imiquimod 5% and imiquimod 3.75% (both compared to placebo) for complete clearance, but the magnitude of effect was greater at higher concentrations and a significant difference in favour of imiquimod 5% was reported for partial clearance [7].

Ingenol mebutate 150mcg/g and 500mcg/g:
Based on pooled data from two similar double-blind RCTs, rates of investigator assessed clearance of AK lesions on the face or scalp 57 days following treatment completion were statistically significantly greater with ingenol 150mg/g than with placebo (42.2% vs. 3.7%; p<0.001; NNT=3). In 108 patients achieving complete clearance with ingenol in these two RCTs 46% remained clear at 12 months follow-up.

Based on pooled data from two similar double-blind RCTs, rates of investigator assessed clearance of AK lesions on the trunk or extremities 57 days following treatment completion were statistically significantly greater with ingenol 500mg/g than with placebo (34.1% vs. 4.7%; p<0.001; NNT=3). In 38 patients achieving complete clearance with ingenol in these two RCTs 50% remained clear at 12 months follow-up [4,6].

Comparative effectiveness:

Direct comparative data for newer agents are limited to the comparison of 5-FU/SA against diclofenac [5]. The Cochrane review includes indirect comparative data for imiquimod 3.75% versus imiquimod 5% [7]. There are no direct comparisons of newer agents available. The SMC advice on ingenol reports brief details of indirect network meta-analyses that suggests there are no statistically significant differences between the newer topical treatments, but due to many differences in trial designs and endpoint assessment these results are subject to considerable uncertainty [4].

Summary of Safety Data:

Established treatments:
Established treatments have a number of common adverse effects listed in their SPCs, including erythema and application site reactions involving pain, swelling, inflammation and pruritis [9-11]. Withdrawal rates from trials due to adverse events were common (e.g. 144 participants per 1000 using diclofenac 3% compared to 40 per 1000 using placebo; 56 participants per 1000 using 5% imiquimod compared to 21 per 1000 using placebo) [7].

Fluorouracil 0.5% + salicylic acid 10%:
The AWMSG guidance on Actikerall® reports that treatment-emergent adverse events occurred more frequently with 5-FU/SA than diclofenac gel in the RCT (95.2% vs.76.8%). The majority were administration site reactions and were mild-to-moderate in severity [5]. Most had cleared by week 20 [8]. The proportion of patients ceasing treatment due to adverse events was low, and similar in the 5-FU/SA and diclofenac gel arms (3.7% and 4.9%, respectively) [5].

Imiquimod 3.75%:
The RDTC report notes that 33.8% of patients using imiquimod 3.75% experienced local skin reactions compared with 1.3% on vehicle placebo in the two RCTs. Erythema scores had returned to baseline by week 10 [8]. The Cochrane review reports that withdrawal rates with imiquimod 5% were greater than with imiquimod 3.75% in indirect comparisons of trial data [7].

Ingenol mebutate:
Local skin reactions occurred in 19% of patients applying ingenol 150mcg/g to the face/scalp and in 12% of patients applying ingenol 500mcg/g to the trunk / extremities, compared with 2.6% applying vehicle placebo in the four RCTs. Reactions peaked between days 3 to 8 and returned to baseline by day 29 [8].

Summary of Evidence on Cost Effectiveness and Patient Outcomes:

Fluorouracil 0.5% + salicylic acid 10%:
The SMC advice [3] provides brief details of a cost utility analysis comparing 5-FU/SA with diclofenac 3% gel in patients with AK over a one-year time horizon. Direct comparative data were taken from the RCT discussed above to model AK lesion clearance rates and recurrence rates measured at week 52 were taken from an uncontrolled follow-up study. Utility values were taken from another study which estimated the cost-effectiveness of two alternative AK treatments, which the SMC considered to be reasonable. Resource use estimates were based on assumption and included one specialist visit to a dermatologist per patient and an additional consultation if a patient experienced recurrence.

The results of the analysis indicated that 5-FU/SA was both more effective (delivering a gain of 0.002 QALYs) and overall less costly (by £32 per patient) than diclofenac 3%, driven by differences in lesion clearance and recurrence rates. However, it is unclear that diclofenac 3% is the most appropriate comparator for 5-FU/SA. Additional analyses estimated 5-FU/SA to be more effective and less costly than fluorouracil 5%. However, this analysis was based on simple indirect comparisons which were noted to have a number of important weaknesses. Despite this, SMC concluded that the economic case for 5-FU/SA had been demonstrated [3].

Imiquimod 3.75%:
No published cost effectiveness analyses of imiquimod 3.75% cream have been identified. The cost per course of treatment is greater than for any of the other established or newer topical treatments (see **Table 2**) and there are no robust data to suggest greater effectiveness, safety or convenience compared with other agents. The licensed indication for imiquimod 3.75% limits its

use to where other topical treatments are contra-indicated or less appropriate [12], as is the case for the 5% concentration [11].

Ingenol mebutate:
The SMC advice [4] provides brief details of a cost utility analysis comparing ingenol mebutate with diclofenac (8 weeks and 12 weeks), and also 5-fluorouracil, and 5-FU/SA over a one year time horizon. As there are no direct comparative data for ingenol mebutate, results of an indirect network meta-analyses, which found no statistically significant difference between treatments for clearance rates, were used in the model. Six months after initiation of first-line therapy it was assumed that patients either responded to treatment and achieved complete clearance that was maintained, or else failed treatment. Ingenol mebutate was estimated to be more effective and marginally more costly overall compared to diclofenac 3% and 5-FU/SA (incremental costs per QALY gained for treatment of face/scalp <£50, and for treatment of trunk/extremities <£150), and to be less costly (by £63) and less effective (by 0.0024 QALYs for face/scalp, and 0.0051 QALYs for trunk/extremities) than 5-fluorouracil [4].

As there were no statistically significant differences in clearance rates estimated in the network meta-analysis, the company provided additional cost minimisation analyses, which estimated that ingenol mebutate would be associated with an additional cost of £0.20 compared diclofenac regimens and 5-FU/SA, but would be less costly than 5-FU by £62. Allowing for recurrence rates and re-treatment increased the additional costs of ingenol mebuate versus diclofenac and 5-FU/Sa to <£9, and increased the cost savings versus 5-FU to £82. Results of the network meta-analysis were subject to considerable uncertainty, the model excluded adverse events and it was assumed that adherence would be identical with all treatments, which may not be the case given that ingenol mebutate has a significantly shorter treatment duration. SMC concluded that the economic case for ingenol mebutate had been demonstrated [4].

Key Points to Note from the Available Evidence:

- The Cochrane review concluded that established topical treatments (diclofenac 3%, imiquimod 5%, 5-fluorouracil 5%) appear to have comparable efficacy and differ with respect to adverse events, but also notes that more direct comparative data are required to determine the best therapeutic approach.
- Comparative data for newer agents is limited to a single trial of 5-FU/SA against diclofenac 3%. This was the only trial of the newer agents to have confirmed lesion clearance histologically. However, the majority of lesions treated in that trial were grade II (hyperkeratotic) for which the Primary Care Dermatology Society indicates diclofenac 3% is the least suitable of the topical treatment options. It is therefore unclear that diclofenac 3% was the most relevant comparator.
- All newer treatments achieved significantly greater complete clearance rates at 8 weeks follow-up compared with placebo (NNTs of 3 or 4). Indirect comparisons of available trial data are reported to show no statistically significant differences between the newer treatments; however, due to many differences in trial designs and endpoint assessment these results are subject to considerable uncertainty.
- All topical treatments are associated with local application site reactions. This may have revealed treatment assignment and biased subjective efficacy assessment in placebo-controlled trials.
- Recurrence rates at 12 months among patients achieving complete AK lesion clearance in the trials of imiquimod 3.75% and ingenol mebutate were high (>50%). Details on recurrence rates with 5-FU/SA are lacking. No data on re-treatment are available.
- The aim of treating AK lesions is to prevent progression to squamous cell carcinoma. Longer term data for newer and established treatments is lacking in this regard.

- The duration and frequency of treatment application for each of the different topical treatments may be expected to influence adverse events, treatment adherence and treatment preferences. Licensed indications differ.

Productivity, Service Delivery and Implementation Considerations:

No impact on service delivery is anticipated.

Innovation, Need and Equity Considerations:

Several established topical treatment options exist for the treatment of AK. None of the newer topical treatments has been robustly demonstrated to be superior to these or each other. A course of treatment with ingenol mebutate is only 2 to 3 days, in contrast to 4 to 12 weeks for other topical treatments (see Table 2), which may be preferred by patients and encourage greater adherence.

There are no anticipated equity considerations.

Recommended Place in Therapy

LMMG recommendations for newer topical treatments for AK:

Ingenol mebutate (Picato®▼) is recommended for the treatment of non-hyperkeratotic, non-hypertrophic AK affecting an area of $\leq 25cm^2$. Ingenol mebutate offers a convenient, short treatment duration and based on current list prices is marginally less costly than diclofenac 3% gel.

Fluorouracil 0.5% + salicylic acid 10% (Actikerall®) is not recommended for the treatment of AK. Limited data suggest it has comparable efficacy to other agents and there is little robust evidence of superior efficacy, safety or convenience versus fluorouracil 5% cream, which has a lower list price.

Imiquimod 3.75% (Zyclara®) is not recommended for the treatment of AK. There is little robust evidence to justify its significantly greater list price compared with other topical treatments.

Financial and Service Implications

Comparative unit costs:
See Table 2 for example comparative unit costs for one course of topical AK treatment.

Anticipated patient numbers and net budget impact:
ePACT data for Lancashire for the year June 2012 to May 2013 [13] indicate that 7,325 items were prescribed with licensed indications that cover AK, at a cost of £286,807. Almost 70% of items were for diclofenac 3% gel, 20% were for fluorouracil 5% cream and 9% were imiquimod 5% cream; prescribing of newer agents is currently low as would be expected. It is difficult to estimate the number of patients treated for AK in Lancashire, as prescribing volumes are dependent on number and type of lesions and need for re-treatment. Fluorouracil 5% cream and imiquimod 5% cream also have licensed indications beyond AK, which may contribute to these figures.

For the treatment of grade I AK (single or few lesions, better felt than seen) the Primary Care Dermatology Society indicates diclofenac 3% is the most suitable of the established topical treatments [2]. Of the newer agents ingenol mebutate and imiquimod 3.75% cream are licensed for non-hyperkeratotic AK. Based on current list prices, ingenol mebutate is less costly than diclofenac 3% gel and so its use may lead to marginal cost savings compared with use of

diclofenac 3% gel. Imiquimod 3.75% is only licensed for use where other agents are contraindicated or are less appropriate and is more costly than all other topical treatments, including imiquimod 5% cream that has a similar AK licensed indication. Current levels of use of imiquimod 5% for treatment of AK is uncertain, but use of imiquimod 3.75% cream instead of imiquimod 5% cream would potentially increase costs by £64 to £129 per course of treatment (see Table 2).

For the treatment of grade II AK (moderately thick, hyperkeratotic lesions, easily felt and seen), the Primary Care Dermatology Society indicates fluorouracil 0.5% + salicylic acid 10% solution, 5% fluorouracil cream or imiquimod 5% cream as the most suitable topical treatment options [2]. Imiquimod is only licensed for use when other topical treatments are less appropriate or contraindicated. Current levels of use of fluorouracil 5% cream for the treatment of AK is uncertain, but use of fluorouracil 0.5% + salicylic acid 10% solution instead of fluorouracil 5% cream would potentially increase costs by £11 to £44 per course of treatment.

Impact of Implementation:

No specific impacts of implementation are anticipated.

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Table 1. Summary of key RCT data for newer topical treatments

Product	Trial designs	Patients	Interventions & Comparator	Primary outcome: Complete clearance	Longer-term follow up
Fluorouracil 0.5% + salicylic acid 10% (Actikerall®) [5]	One phase III, double-blind RCT	470 adults with 4 to 10 AKs on their face, forehead or bald scalp. 40% of AKs grade I (mild); (60%) grade II (moderate).	5-FU/SA once daily, diclofenac gel twice daily vs. placebo vehicle until all lesions cleared or for a maximum of 12 weeks	Histological clearance for one representative AK lesion 8 weeks after treatment: 72.0% vs. 59.1% ($p < 0.01$; NNT=8 vs. diclofenac)	No longer term follow-up from this trial
Imiquimod 3.75% (Zyclara®) [8]	Two identical RCTs	479 adults with 5 to 20 lesions on the face or scalp	Imiquimod 3.75% or placebo to be applied once daily for two two-week cycles separated by a two-week treatment-free interval. Up to two sachets (250 mg each) were applied per dose	Investigator assessed complete clearance 8 weeks after treatment finished 35.6% of imiquimod 3.75% recipients vs. 6.3% of placebo recipients ($p<0.001$; NNT=3).	In patients achieving complete clearance in these two RCTs and two other RCTs that used a different treatment regimen, 40.5% remained clear at 12 months follow-up
Ingenol mebutate 150mg/g (Picato®▼) 4,6]	Two similar double-blind RCTs	547 adults with 4 to 8 typical AK lesions covering area $\leq 25cm^2$ on face or scalp	Ingenol mebutate 150mg/g of vehicle placebo applied to a $25cm^2$ area once daily for three consecutive days	Investigator assessed complete clearance 57 days after treatment finished 42.2% vs. 3.7% ($p < 0.001$; NNT=3)	In 108 patients achieving complete clearance with ingenol in these two RCTs 46% remained clear at 12 months follow-up
Ingenol mebutate 500mg/g (Picato®▼) [4,6]	Two similar double-blind RCTs	458 adults with 4 to 8 typical AK lesions covering area $\leq 25cm^2$ on trunk or extremities	Ingenol mebutate 500mg/g of vehicle placebo applied to a $25cm^2$ area once daily for three consecutive days	Investigator assessed complete clearance 57 days after treatment finished 34.1% vs. 4.7% ($p<0.001$; NNT=3)	In 38 patients achieving complete clearance with ingenol in these two RCTs 50% remained clear at 12 months follow-up

Table 2. Comparison of licensed indications and acquisition costs for topical AK treatments

Treatment	Licensed AK indication	Treatment regimen / course	Pack cost	Cost per course (ex VAT)
Diclofenac 3% gel (Solaraze®) [9]	Actinic keratosis	Applied twice daily for 60 to 90 days. Maximum of 8 grams daily	50g = £38.30	£76.60*
Fluorouracil 5% cream (Efudix®) [10]	Keratoses including actinic forms	Applied once or twice daily	40g = £32.90	£32.90 to £65.80*
Imiquimod 5% cream (Aldara®) [11]	Clinically typical, non-hyperkeratotic, non-hypertrophic AK on the face or scalp in immunocompetent adults when the size and number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate	Applied three times per week for 4 weeks, repeated after a 4 week break if necessary	12 x 250mg sachets = £48.50	£48.60 to £97.20
Fluorouracil 0.5% + salicylic acid 10% solution (Actikerall®) [14]	Slightly palpable and/or moderately thick hyperkeratotic AK (grade I / II) in immunocompetent adults	Applied once daily. Response can be seen as early as 6 weeks. Response increases over time and data are available for up to 12 weeks. Maximum treatment are 25cm^2.	25ml = £38.30	£76.60*
Imiquimod 3.75% cream (Zyclara®) [12]	Clinically typical, nonhyperkeratotic, nonhypertrophic, visible or palpable actinic keratosis (AK) of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate	Applied once daily before bedtime for two treatment cycles of 2 weeks each separated by a 2-week no-tretament cycles. Treatment area is the full face or balding scalp. Maximum of 2 sachets per application	28 x 250mg sachet = £113.00	£113.00 to £226.00
Ingenol mebutate 150mcg/g gel (Picato®▼) [15]	Non-hyperkeratotic, non-hypertrophic AK in adults	AK on the face / scalp: One tube of Picato 150 mcg/g gel (containing 70 mcg ingenol mebutate - for treating area of 25cm^2) should be applied once daily to the affected area for 3 consecutive days.	3 tubes = £65.00	£65.00
Ingenol mebutate 500mcg/g gel (Picato®▼) [16]		AK on the trunk / extremities: One tube of Picato 500 mcg/g gel (containing 235 mcg ingenol mebutate - for treating are of 25cm^2) should be applied once daily to the affected area for 2 consecutive days	2 tubes = £65.00	£65.00
Costs based on MIMS list prices, July 2013. * Costs per course based on treating a 25cm^2 area for 12 weeks. Full treatment response may be delayed by several weeks beyond end of treatment. See relevant SPCs for full dosing details. This table does not imply therapeutic equivalence of drugs or doses.				

Staffordshire and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR
Tel: 01772 644 400 | www.staffordshirelancashirecsu.nhs.uk